NIDCR Guide for

Data and Safety Monitoring Boards

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* With this issuance, the NIDCR updates its policies and procedures relative to Data and Safety Monitoring Boards

INTRODUCTION

The policy of the National Institute of Dental and Craniofacial Research (NIDCR) is to establish Data and Safety Monitoring Boards (DSMBs) for Institute-supported clinical trials when an independent committee of experts is required to ensure the safety of participants and the integrity of the trial.

All grants, cooperative agreements, and contracts that require DSMBs should include administrative and budgetary provisions for these Boards. DSMB plans should be included in the application/proposal but, if necessary, may be added at the time of award through a noncompetitive supplement. The NIDCR Program Official, on behalf of the Institute, will review plans for DSMBs to ensure that they are adequate and that Board operations are independent of investigators involved in the study. Funds for the study will not be released until DSMB plans have been reviewed and approved by the NIDCR Program Official.

As a general rule, logistical and budgetary (via the grant) support for Board operations will be the responsibility of the trial Principal Investigator or Study Chairperson. However, under certain circumstances the Institute may elect to directly administer and reimburse for Board operations. Irrespective of the means of logistical and budgetary support for Board operations, all DSMBs for NIDCR-sponsored clinical trials will be appointed in consultation with the NIDCR Program Official and report directly to the Director of the Institute through the Program Offical.

This guide has been developed to assist clinical trial Principal Investigators and Data and Safety Monitoring Board members in understanding NIDCR policies and practices relative to DSMBs. The document covers the establishment, roles and responsibilities, as well as meeting, deliberation, and recommendation processes of Boards. Responsibilities of clinical trial Principal Investigators or Study Chairpersons (for multi-center trials) in facilitating Board functions are also included.

DSMBs for NIDCR-sponsored Clinical Trials

Background

Pursuant to NIH policy, every clinical trial **must** have provision for data and safety monitoring. The method and degree of monitoring is predicated on participant risk, as well as the size and complexity of the trial. NIH requires all multi-center clinical trials involving interventions that entail potential risks to participants to have a Data and Safety Monitoring Board (DSMB). All Phase III clinical trials as well as many Phase I/II clinical trials that involve potential risks to participants will require a Data and Safety Monitoring Board, irrespective of the number of participating centers.

Prior to making an award for a clinical trial, NIDCR staff will review the method and degree of monitoring proposed by the Principal Investigator (PI) or Study Chairperson, as applicable, to ensure that it is appropriate for the degree of risk involved. If needed, adjustments will be made to safety monitoring plans prior to making an award. If a DSMB is needed to adequately ensure participant safety, the NIDCR will rely on Board members to review the trial protocol, to review the data and safety monitoring plans, to monitor data as they accumulate, and to make recommendations to the Institute regarding appropriate protocol and operational changes.

The following guidelines define the roles and responsibilities of DSMBs for NIDCR-supported clinical trials.

Guidelines

1. DSMB Role

The NIDCR and DSMBs must ensure that patients are not exposed to unreasonable or unnecessary research risks. As such, trials should not continue beyond the point when the question posed appears to be answered, when valid conclusions regarding study endpoints are unlikely, or when serious adverse events are identified. DSMBs may recommend to the NIDCR the termination of a study because of apparent efficacy, poor study progress, or serious adverse events/toxicities.

DSMBs have primary responsibility for monitoring treatment effects and therefore must use their collective judgment in reviewing interim data in the context of the most recent scientific literature and determine if there is convincing evidence to stop or continue the study. It is anticipated that DSMBs will use their own expertise and a broad array of information to assess interim evidence from the trial and to make recommendations. Information used by the DSMB to protect the interest and safety of trial participants and the scientific integrity of the trial include: stopping guidelines, evidence from outside the study, and important aspects of the trial including accrual and follow-up, data quality, protocol

adherence, safety, convincing evidence of treatment effects or the lack thereof, study integrity, and resources.

DSMB oversight includes review and approval of the trial protocol prior to participant accrual as well as review and approval of protocol changes and ancillary studies prior to their implementation. Once convened, the Board will report directly to the Director of the Institute through the Program Official. All Board recommendations and "action items" will be contained in the minutes of the Boa proceedings. These will be forwarded to the Program Offical who, in turn, will insure that the Principal Investigator or Study Chairperson, as applicable, receives copies of recommendations and/or action items in a timely manner

2. Reimbursement

DSMBs should be intellectually and financially independent of trial investigators and institutions. Reimbursement of members for DSMB participation must be provided by the grantee or contractor from funds restricted for this purpose in such a manner as to maintain the independence of the DSMB. For multi-center trials, the Data Coordinating Center may undertake this task. Reimbursements must be made with the concurrence of the NIDCR Program Official.

3. Conflict of Interest

DSMB members must have no vested interest in the outcome of the trial including financial ties to any commercial concerns likely to be affected. Their independence must be documented in Conflict of Interest Statements submitted by DSMB members at the time they are asked/agree to serve on the Board and annually thereafter. It is the responsibility of the Principal Investigator or Study Chairperson to obtain and update Board member conflict of interest statements as required.

4. Members

Once a grant, cooperative agreement, or contract proposal has been reviewed and the NIDCR anticipates funding, the Principal Investigator or Study Chairperson may nominate Board members for concurrence by the NIDCR Program Offical. Individuals should be nominated as voting members based on their scientific accomplishments, ability to attend meetings and to work in groups as well as within the guidelines of all applicable NIDCR and NIH policies and procedures. Proposed members must be screened for potential conflicts of interest such as financial ties to any commercial concerns likely to be affected by the outcome of the trial or for extensive collaborative research with the investigators participating in the study. Board members should not be from, or recently affiliated with the same institution(s) as the Principal Investigator or Study Chairperson.

To obtain approval of the proposed members, the Principal Investigator or Study Chairperson should forward a list of individuals to the NIDCR Program Official. The list should identify, where applicable, the first and alternate choice for each DSMB slot and briefly describe the factors supporting the nominations. Potential Board members should be contacted only after appropriate screening for potential conflicts has been undertaken and NIDCR concurrence with the appointment has been obtained.

Depending on the size and complexity of the clinical trial, the typical DSMB will consist of between five and ten voting members with expertise in ethics, biostatistics, trial methodology, and specialty areas of dentistry, medicine, and laboratory sciences. At least some Board members should have previous experience serving on trial monitoring boards.

The Chairperson of the DSMB should have clinical research experience and a demonstrated ability to lead meetings and engage groups in full discussion of relevant issues.

Non-voting/ex-officio members of DSMBs for NIDCR-sponsored clinical trials will include, but not be limited to, an NIDCR Program Official and a representative of the study's Data Coordinating Center, where applicable.

5. Meetings

The Principal Investigator (PI) or Study Chairperson is responsible for all logistical and budgetary (via the grant) support necessary for Board operations including meetings, conference calls, mailings and minutes. For multi-center trials, the Study Chairperson may, with the approval of the NIDCR Program Official, delegate these tasks to the Data Coordinating Center.
(Prior to the first Board meeting, the PI should inform Board members of the procedures for handling the reimbursement of travel expenses.)

While DSMB meetings should be scheduled at intervals commensurate with anticipated need, DSMBs should meet in-person at least once a year. Interim meetings and conference calls should be scheduled as necessary.

DSMB voting members, the NIDCR Program Official, a representative of the study's Data Coordinating Center, and other ex-officio Board members, as applicable, should attend all DSMB meetings and participate in all Board monitoring and decision-making activities. If required, consultants and study investigators may be invited to specific meetings but they may not vote.

All requisite DSMB meeting materials including the study protocol, manual of operations, IRB approvals, draft stopping guidelines, ongoing data reports, and responses to Board recommendations or "action items" must be forwarded by the Principal Investigator or Study Chairperson to voting members of the Board, the NIDCR Program Official, and other ex-officio Board members at least fourteen days

before the initial meeting and/or subsequent meetings, as applicable, unless otherwise requested by the Board.

It is the responsibility of the Principal Investigator or Study Chairperson to report all adverse events in a timely manner to the Board, the NIDCR Program Official, participating Internal Review Boards, as well as the FDA and IND holder, if applicable.

It is also the responsibility of the Principal Investigator or Study Chairperson to submit for review and approval by the Board all significant protocol changes and ancillary study proposals prior to their implementation.

To ensure smooth and effective operations, a number of issues should be addressed at the initial meeting of the Board. Topics to be discussed prior to the review of trial data include policies and procedures for: developing meeting agendas and reaching recommendations, as well as for determining that the trial should be stopped or investigators unmasked. A basic format for presentation of ongoing data and the timeframe in which the data must be provided as well as an approach to utilizing stopping guidelines should also be part of initial Board deliberations.

Focusing primarily on issues of patient protection and study integrity, the DSMB should review the final protocol, manual of operations, and proposed ancillary studies during their initial meeting.

Each Board meeting should be divided into several parts. First, an open session in which members of the clinical trial team may be present, at the request of the DSMB, to review the conduct of the trial and to answer questions from members of the Board. The focus in the open session may be on accrual, protocol compliance, and general discussion of adverse events. Outcome results must not be discussed during this session.

Following the open session, a closed session involving DSMB members and the statistician(s)/coordinating center staff handling the trial may be held to discuss outcome results as applicable

Finally, an executive session involving only DSMB members (voting and ex-officio) should be held to further discuss the general conduct of the trial and all outcome results including adverse events and toxicities. At the end of each executive session, voting members of the DSMB should make a recommendation to the NIDCR regarding continuation of the trial. The NIDCR Program Official, serving as an ex-officio Board member, will participate in all sessions of the Board in an advisory capacity.

6. Minutes

The Principal Investigator or Study Chairperson is responsible for assuring that there is an independent means of preparing minutes for each Board meeting and/or conference call. Proposed arrangements for minute-taking must be cleared with the Board Chairperson and the NIDCR Program Official well in advance of each meeting. For multi-center trials, the Data Coordinating Center may be delegated this

task.

The minutes of DSMB meetings should include: highlights of meeting discussions, general recommendations, action items, suggested protocol changes, and the rationale behind Board these. Confidential data should not be included in the minutes. The proposed date of the next regularly scheduled meeting should be listed at the end of the minutes.

Draft minutes should be reviewed by the Board Chairperson and the NIDCR Program Official for accuracy. Final copies of the minutes must be forwarded to the NIDCR Program Official and the Board Chairperson within 30 days after the meeting. The NIDCR Program Official will send action items, recommendations and other relevant excerpts to the Principal Investigator or Study Chairperson.

7. Recommendations to NIDCR

DSMB members must be satisfied that the timeliness and accuracy of data submitted to them for review are sufficient to protect the safety and health of trial participants. Failure of investigators to provide such data will result in a recommendation to the NIDCR to discontinue the trial until a satisfactory response is received.

DSMB recommendations should be made to the NIDCR in writing no more than five working days after the DSMB meeting, but recommendations for major changes should be communicated verbally immediately. The NIDCR will act on recommendations in a timely manner.

The NIDCR will address safety and/or quality concerns expressed by the Board (e.g., by extending the period of recruitment, modifying the protocol in collaboration with the trial Principal Investigator or Study Chairperson or discontinuing a study with safety concerns or poor performance). In the event that the Institute may need an independent evaluation of the Board's recommendation it may wish to establish an ad hoc committee which could include initial reviewers, DSMB members, and other relevant consultants.

8. Recommendations to the Principal Investigator

In addition to recommendations to the NIDCR, the DSMB may make recommendations to the Principal Investigator or Study Chairperson and request follow-up information to be submitted to the Board. These may include, but are not limited to, the following:

- ethical aspects of the trial, with particular attention to the rights and welfare of human subjects;

- overall progress of the trial (e.g., patient enrollment, adherence to the study protocols, safety and efficacy of treatment underway and completeness of follow-up) and proposed major changes in the trial protocol;

- appropriateness of proposed protocol changes and ancillary studies;

- the need to change the treatment protocol, terminate the trial, extend the trial or change elements in the trial design; and

- ongoing and issue-specific reports to be reviewed by the DSMB.

9. Confidentiality

All materials, discussions and proceedings of the DSMB are completely confidential. Members and other participants in DSMB meetings are expected to maintain the confidentiality principle.

Additional Important Information for Applicants

1. Interim Analyses and Multiple Statistical Tests

Reviews of study data by DSMBs may involve interim statistical analyses on an annual basis. Applicants are advised to take this possibility into account in determining study sample size in order to insure that multiple statistical tests do not adversely affect the probability of making a Type I error and/or reducing the power of the statistical tests used in the analysis.

2. *DSMBs for Co-funded Studies*

For studies co-funded with another ICD, the decision to appoint a DSMB would generally be made by the lead ICD. The oversight of the DSMB will be implemented collaboratively.